REMARKS

1. Preliminary Remarks

a. Status of the Claims

Claims 21-48 and 50-55 are pending in this application. Claims 35-48, 51, 54, and 55 have been withdrawn as being drawn to a non-elected invention. Claims 21 and 35 have been amended. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present application. Upon entry of these amendments, claims 21-34, 50, 52, and 53 will be pending and under active consideration.

b. Priority

On page 3 of the Office Action, the Examiner denies the priority claim on the ground that none of the prior-filed applications provide adequate support or enablement for the claimed molecular structure as set forth in SEQ ID NO: 2079. Applicant respectfully disagrees.

Claims 21-34, 50, 52 and 53 are directed to a genus of viral miRNAs that are disclosed in the priority applications. The Examiner objects to the priority claim solely on the basis of SEQ ID NO: 2079. Applicant notes that claim 21 and its dependent claims related to a genus of viral miRNAs are entitled to the filing date of the priority applications.

c. Amendment to the Claims

Claim 21 has been amended to clarify that the sequence of the claimed nucleic acid is present within a viral genome. Specifically, claim 21 is amended to recite that a viral genome comprises the claimed nucleic acid (i.e., the "first viral nucleic acid") and also the referenced "second viral nucleic acid." Withdrawn claim 35 has been similarly amended.

With respect to claim 21, the "first viral nucleic acid" are miRNA-related nucleic acids, which are relatively short nucleic acids of 15-24 nucleotides. The "second viral nucleic acid" includes hairpin precursors of miRNAs. The precursors are longer nucleic acids of 50 to131 nucleotides that are capable of forming a stem-loop structure. The hairpin precursor may be processed to yield the shorter miRNA. The hairpin precursor (i.e., the "second viral nucleic acid"), therefore, comprises the miRNA (i.e., the "first viral nucleic acid").

Whereas claim 21 is drawn to miRNA-related nucleic acids, claim 35 is drawn to hairpin precursors of miRNA-related nucleic acids. As a result, the "first viral nucleic acid" of claim 35 refers to the hairpin precursor whereas the "second viral nucleic acid" refers to the miRNA-related nucleic acids. As discussed throughout the specification, such as at page 4, line 28 to page 5, line 20,

each of the claimed miRNAs and related hairpin precursors were identified within the genomic sequences of various viruses. Therefore, the application as originally filed provides support for a viral genome comprising the sequence of each of the disclosed hairpin precursors and miRNA-related nucleic acids. Minor grammatical errors outlined by the Examiner on page 2 of the Office Action have also been corrected.

d. Objection to the Claims Request of Rejoinder

The Examiner further objects to claim 50 for being directed to non-elected subject matter. Applicant submits that upon allowance of the generic claim 21, the non-elected subject matter will then be entitled to examination.

e. Interview

The undersigned would like to thank Examiner Shin and Examiner Angell for the courtesy of the personal interview on December 23, 2009 (hereafter "the Interview") during which the written description and prior art rejections were discussed as well as possible amendment to the claims. This Reply is filed to address in part the issues raised by the Examiners.

2. Patentability Remarks

a. 35 U.S.C. §112, Second Paragraph, Indefiniteness

On pages 4 and 5 of the Office Action, the Examiner rejects claims 21-34, 50, 52, and 53 under 35 U.S.C. §112, second paragraph, for allegedly being indefinite. The Examiner asserts that the claims do not particularly point out why the claims recite two different nucleic acids (a first nucleic acid and a second nucleic acid) when the claims are only directed to the first nucleic acid, and therefore one of skill cannot determine the structural/functional relationship between the first and second nucleic acid. Applicant respectfully disagrees.

As discussed above, with respect to claim 21, the "first viral nucleic acid" are miRNA-related nucleic acids, which are relatively short nucleic acids of 15-24 nucleotides. The referenced "second viral nucleic acid" includes hairpin precursors of miRNAs. The precursors are longer nucleic acids of 50 to 131 nucleotides that are capable of forming a stem-loop structure. The hairpin precursor may be processed to yield the shorter miRNA. The sequence of the hairpin precursor (i.e., the "second viral nucleic acid"), therefore, comprises the sequence of the miRNA (i.e., the "first viral nucleic acid"). As discussed throughout the specification, each of the claimed miRNAs were identified from the genomic sequences of various viruses. Therefore, a viral genome comprises the sequence of each of the claimed miRNA-related nucleic acids and the related hairpin precursors.

Claim 21 is directed to a "first viral nucleic acid," which is a viral miRNA-related nucleic acid. The reference in claim 21 to the "second nucleic acid" reduces the scope of the claim by requiring that the sequence of the first nucleic acid be present within the sequence of a viral hairpin precursor sequence. Furthermore, claim 21 recites that the sequence of both the miRNA-related nucleic acid and the hairpin precursor are present in a viral genome. In view of the foregoing, Applicant submits that one of ordinary skill in the art clearly would identify the scope of the claim 21 and would understand the metes and bounds of the subject matter that will be protected. Therefore, Applicant respectfully asserts that the rejection of claims 21-34, 50, 52, and 53 under 35 U.S.C. §112, second paragraph, has been overcome and request withdrawal of the same.

b. 35 U.S.C. §102(e), Anticipation

On pages 5-15 of the Office Action, the Examiner rejects claims 21, 22, 25, 33, 34 and/or 50 under 35 U.S.C. §102(e) as being anticipated by Zamore (U.S. Patent App. Pub. No. 2006/0009402; hereafter "Zamore"), Cullen et al. (U.S. Patent Appl. Pub. No. 2004/0053411; hereafter "Cullen"), Khvorova et al. (U.S. Patent Appl. Pub. No. 2007/0031844; hereafter "Khvorova"), Usman (U.S. Patent Appl. Pub. No. 2005/0124568; hereafter "Usman"), Stacey (WO 00/31540; hereafter "Stacy"), Berlin (WO02/077272; hereafter "Berlin"), Baker (U.S. Patent No. 6,399,297; hereafter "Baker"), Lieven (U.S. Patent No. 6,087,093; hereafter "Lieven"), Zhu et al., J. of General Virology 73:1309-1312 (1992; hereafter "Zhu"), Ghiringhelli *et al., J. of General Virology* 72:2129-2141 (1991; hereafter "Ghiringhelli"), Baumstark *et al., RNA* 7:1652-1670 (2001; hereafter "Baumstark"), Ozadarendeli *et al., J. of General Virology* 75:7362-7374 (2001; hereafter "Ozadarendeli"), and Davison *et al., J. of General Virology* 66:207-220 (1985; hereafter "Davison").

Non Viral miRNA related Sequence--Zamore, Cullen, Khvorova, Stacey, Berlin, Baker, and Lieven

As a preliminary matter, the Examiner asserts that "viral nucleic acid" in the preamble of claims 21 and 35 is interpreted as including a nucleic acid that targets and modulates viral nucleic acid when the claims are given its broadest reasonable interpretation. In other words, the Examiner interprets the claimed nucleic acid to be from any source. Applicant has previously argued that the preamble and the previous language in the wherein clause requiring the nucleic acid to be "isolated from the genome of a virus" required the claimed sequence to be present in the genome of the virus. Such a feature distinguishes the claimed nucleic acids over the cited references, which disclose either synthetic or eukaryotic sequences such as human. The Examiner interpreted that the previous language of "isolated from the genus of a virus" as a "process" step and, therefore, does not patentably distinguish the nucleic acids of Zamore, Cullen, Khvorova, Stacey, Berlin, Baker and

Lieven because patentability is based upon the product itself. In response, claim 21 and its dependents 22, 25, 30 (probe), 34 (vector) and 50 have been amended to recite that a viral genome comprises the sequence of the claimed nucleic acid (i.e., the "first viral nucleic acid") and also the sequence of the referenced hairpin precursor (i.e., the "second viral nucleic acid"), as discussed above.

Viral Genomic Regions—Zhu, Ghiringhelli, Baumstark, Ozadarendeli, Davison

With respect to the remaining references cited under § 102(b), the Examiner has misinterpreted the scope of claim 21. Claim 21 is related to a nucleic acid that is 15-24 nucleotides in length. As discussed in detail below, each of the nucleic acids cited in Zhu, Ghiringhelli, Baumstark, Ozadarendeli and Davison are larger than the 15-24 nucleotides of the claimed miRNA-related viral nucleic acids.

Zhu

On pages 12 and 13 of the Office Action, the Examiner rejects claims 21 and 52 under 35 U.S.C. § 102(b) as allegedly being anticipated by Zhu *et al.* (Journal of General Virology, 1992;73:1309-12)("Zhu" hereafter). The Examiner asserts that Figure 2 of Zhu discloses a nucleic acid isolated from nucleotides 1010-1055 of the intergenic, non-coding region of a rice stripe virus isolate T RNA 4, wherein the nucleic acid contains a "first viral nucleic acid" of 18-24 nucleotides. The Examiner further asserts that the nucleic acid of Zhu meets the structural requirements of the nucleic acids of claims 21 and 52. Applicant respectfully disagrees.

Applicant submits that the Examiner has misconstrued the scope of claims 21 and 52, and of the prior art. The isolated nucleic acid of claim 21 is 15-24 nucleotides in length, and that of claim 52 is 18-24 nucleotides. Thus, the isolated nucleic acids of claims 21 and 52 **cannot exceed 24 nucleotides in length**. The Examiner asserts that the sequences shown in Figure 2 of Zhu meet the structural limitations of claims 21 and 52, however, this figure depicts only a portion of RSV-T RNA 4. RSV-T RNA 4 is 2157 nucleotides long. *See* Zhu at page 1309, column 2 ("The cDNA covering the full length of the RNA 4 segment was obtained by primer extension") *and* at page 1311, column 1 ("RSV-T RNA 4 consists of 2157 nucleotides…"). Thus, the entire length of the nucleic acid disclosed by Zhu is more than 24 nucleotides. Moreover, the Examiner characterizes the sequence in Figure 2 of Zhu as being nucleotides 1010-1055 of RSV-T RNA 4, which is 46 nucleotides in length. The other sequence shown in Figure 2 is 36 nucleotides in length. Thus, both sequences depicted in Figure 2 are longer than 24 nucleotides, and therefore fail to meet all of the limitations of claims 21 and 52. Accordingly, Zhu does not anticipate these claims.

Ghiringhelli

On page 13 of the Office Action, the Examiner rejects claims 21 and 52 under 35 U.S.C. § 102(b) as allegedly being anticipated by Ghiringhelli *et al.* (Journal of General Virology, 1991;72:2129-41)("Ghiringhelli" hereafter). The Examiner asserts that Figure 6 of Ghiringhelli discloses two nucleic acids isolated from the intergenic, non-coding region of a Junin virsus S RNA, where each of the two nucleic acids contains a "first viral nucleic acid" of 15-24 nucleotides or 18-24 nucleotides. The Examiner further asserts that these two nucleic acids of Ghiringhelli meet the structural requirements of the nucleic acids of claims 21 and 52. Applicant respectfully disagrees.

As discussed above, the nucleic acids of claims 21 and 52 **cannot exceed 24 nucleotides in length**. The Examiner asserts that sequences shown in Figure 6 of Ghiringhelli meet the structural limitations of claims 21 and 52, however, this figure depicts only a portion of Junin S RNA. This S RNA is 3400 nucleotides long, and was cloned in fragments at least approximately 500 nucleotides long. *See* Ghiringhelli at page 2131, column 1 *and* at Figure 2 (showing overlapping clones of the full-length S RNA, where the shortest, pJUN9 is around 500 nucleotides long, and the rest are at least 1 kb-long). Thus, the entire length of Junin S RNA is more than 24 nucleotides. Moreover, the sequence shown in Figure 6 is 121 nucleotides in length. *See* Ghiringhelli at Figure 6 ("A portion of the S RNA (nucleotides 1519 to 1639)… is shown"). Thus, even the sequence cited by the Examiner exceeds 24 nucleotides in length, and therefore fails to meet all of the limitations of claims 21 and 52. Accordingly, Ghiringhelli does not anticipate the claims.

Baumstark

On pages 13 and 14 of the Office Action, the Examiner rejects claims 21 and 52 under 35 U.S.C. § 102(b) as allegedly being anticipated by Baumstark *et al.* (RNA, 2001;7:1652-70) ("Baumstark" hereafter). The Examiner asserts that Baumstark discloses nucleic acids isolated from the intergenic regions of bromovirus RNA 3, CMV subgroups I and II, and TAV, wherein each of the nucleic acids has a hairpin structure and comprises a "first viral nucleic acid" of 15-24 nucleotides or 18-24 nucleotides. The Examiner further asserts that Figure 7 of Baumstark discloses nucleic acids that meet the structural requirements of the nucleic acids of claims 21 and 52. Applicant respectfully disagrees.

As discussed above, the nucleic acids of claims 21 and 52 **cannot exceed 24 nucleotides in length**. The Examiner asserts that Figure 7 of Baumstark discloses sequences that meet the structural limitations of claims 21 and 52, however, this figure depicts only a portion of longer IGR sequences from different types of viruses. Baumstark discloses IGR-related sequences that all

exceed 24 nucleotides in length. Specifically, IGRcp is 321 nucleotides long, IGR is 219 nucleotides long, and $IGR^{delta\text{-}14}$ is 205 nucleotides long. *See* Baumstark at Figure 1 *and* page 1653, column 2. Thus, the entire lengths of the sequences disclosed by Baumstark are more than 24 nucleotides. Moreover, all of the sequences shown in Figure 7 are approximately 64 nucleotides in length. *See* Baumstark at Figure 7A (showing a consensus sequence spanning from about nucleotides 1073 to 1136). Thus, the sequences cited by the Examiner are longer than 24 nucleotides, and therefore fail to meet all of the limitations of claims 21 and 52. Accordingly, Baumstark does not anticipate the claims.

Ozdarendeli

On page 14 of the Office Action, the Examiner rejects claims 21, 52, and 53 under 35 U.S.C. § 102(b) as allegedly being anticipated by Ozdarendeli *et al.* (Journal of General Virology, 2001;75:7362-74)("Ozdarendeli" hereafter). The Examiner asserts that Ozdarendeli discloses nucleic acids isolated from the intergenic region of bovine coronavirus, where the nucleic acids have a stable stem-loop hairpin secondary structure and comprise a first viral nucleic acids of 18-24 nucleotides. The Examiner further asserts that Figure 2A of Ozdarendeli discloses nucleic acids that meet the structural requirements of the nucleic acids of claims 21, 52, and 53. Applicant respectfully disagrees.

The nucleic acids of claims 21, 52, and 53 **cannot exceed 24 nucleotides in length**. The Examiner asserts that Figure 2A of Ozdarendeli discloses sequences that meet the structural limitations of claims 21, 52, and 53, however, this figure depicts only a portion of a longer mRNA 5 IS region. The mRNA 5 IS region is 199 nucleotides long. *See* Ozdarendeli at page 7365 ("To test for the existence of the predicted helical region, enzyme structure probing was done on the isolated 199-nt-long IS-containing region (Fig. 2A and B)") *and* at Figure 2A. Thus, this sequence is longer than 24 nucleotides. Moreover, the sequence shown in Figure 2A is 134 nucleotides long. Thus even the sequence cited by the Examiner is longer than 24 nucleotides, and therefore fails to meet all of the limitations of claims 21, 52, and 53. Accordingly, Ozdarendeli does not anticipate the claims.

Davison

On pages 14 and 15 of the Office Action, the Examiner rejects claims 21, 52, and 53 under 35 U.S.C. § 102(b) as allegedly being anticipated by Davison *et al.* (Journal of General Virology, 1985;66:207-20)("Davison" hereafter). The Examiner asserts that Davison discloses a hairpin nucleic acid isolated from the non-coding intergenic region HSV-1 and a hairpin nucleic acid isolated from the non-coding intergenic region of VZV, where each of the two hairpin nucleic acids

contains a "first viral nucleic acid" of 18-24 nucleotides. The Examiner further asserts that Figure 6 of Davison discloses nucleic acids that meet the structural requirements of the nucleic acids of claims 21, 52, and 53. Applicant respectfully disagrees.

As discussed above, the nucleic acids of claims 21, 52, and 53 **cannot exceed 24 nucleotides in length**. The Examiner asserts that Figure 6 of Davison discloses sequences that meet the structural limitations of claims 21, 52, and 53, however, this figure depicts only a portion of a far longer pieces of VZV and HSV-1 genomic DNA. The VZV genomic DNA fragments disclosed by Davison are 400 to 1500 nucleotides in length, and are themselves derived from even longer isolated nucleic acids of 6795 and 2841 nucleotides. *See* Davison at page 208, methods ("The DNA sequences of [VZV genome portion] *SstI f* (6795 bp) and *KpnI l* (2841 bp) were derived respectively from approx. 70000 and 18000 nucleotides of data…. Most M13 clones were made by sonicating plasmid DNA and inserting random fragments (400 to 1500 bp) into the *SmaI* site of M13 mp8"). Thus, the entire lengths of the nucleic acids specifically disclosed by Davison are more than 24 nucleotides. Moreover, the sequences in Figure 6 are, respectively, 46 and 40 nucleotides in length. Thus, even the sequences cited by the Examiner are longer than 24 nucleotides, and therefore fail to meet all of the limitations of claims 21, 52, and 53. Accordingly, Davison does not anticipate the claims.

c. 35 U.S.C. §103(a), Obviousness

On page 7 of the Office Action, the Examiner rejects Lai *et al*, *Genome Biology* 4:R42 (2003; hereafter "Lai"), in view of Zhu, Ghiringhelli, Baumstark, Ozdarendeli, Davison, and Perry *et al., J. of General Virology* 69:2831-2846 (1988; hereafter "Perry"). Specifically, the Examiner asserts that absent secondary considerations, one of ordinary skill in the art at the time of the invention would utilize a computational algorithm-based bioinformatics methodology (such as Lai) to identify potential miRNAs located within the non-codigin regions of viral genomes such as the non-coding regions of rice stripe virus T-RNA 4 (Zhu), Junin virus S (Ghiringhelli), Bromovirus RNA 3 (Baumstark), CMV subgroups I and II (Baumstark), TAV (Braumstark), PSV (Braumstark), Bovine coronavirus (Ozdarendeli), Varicella-Zoster Virus (Davison), Herpes Simplex Virus Type 1 (HSV-1)(Davison and Perry), and isolated these miRNAs from these viral genomes. Similar to previous obviousness rejections on the record, Applicant once again overwhelmingly shows that the Examiner has failed to show that one of skill would have an expectation to succeed in this endeavor.

The evidence that the Applicant has presented on the record includes in part that at the time of filing, miRNAs and hairpin precursors were believed to be present in only complex eukaryotes

(see Reply filed February 26, 2008.); algorithms such as those taught in Lai for predicting secondary structures such as hairpin precursors were based upon hairpins and miRNAs identified in higher eukaryotic model organisms (See reply filed March 16, 2009); and the known viral genomes were too small and had little intergenic space to harbor hairpin precursors in view of the known hairpin frequency in divergent plant and eukaryotic organisms (see Reply filed February 26, 2008).

In response to this evidence supporting non-obviousness, the Examiner asserts that different viral genomic sequence have differing lengths/spaces of intergenic regions and that the intergenic space of HSV-1 contains sufficient space to harbor hairpin precursors. Furthermore, the Examiner asserts that the Applicant has failed to provide **any** compelling evidence showing that there would have been **absolutely no possibility** of finding miRNAs in a viral genomic sequence, or that miRNAs are only found in genetically related organisms. The Examiner concludes that in view of the fact no viral miRNAs had been isolated at the time of filing, and some viral genomic sequences contained lengthy non-protein coding intergenic sequence regions, one of skill would have been motivated and expected to successfully identify miRNAs from non-protein coding sequences of a viral genome utilizing art-recognized bioinformatic-based miRNA identification tools. Therefore, the Examiner further concludes that no illogically "high" level of "creativity" is deemed necessary to arrive at the claimed invention as asserted by the Applicant.

Applicant submits that the Examiner is using an improper standard with regard to the consideration of the Applicant's evidence that it was unpredictable to identify and isolate viral miRNAs by one of skill in the art at the time of filing. The evidentiary standard for obviousness is articulated in MPEP 2142, which states the following (emphasis added):

> If the examiner determines there is factual support for rejecting the claimed invention under 35 U.S.C. 103, the examiner must then consider any evidence supporting the patentability of the claimed invention, such as any evidence in the specification or any other evidence submitted by the applicant. The ultimate determination of patentability is based on the entire record, by a **preponderance of evidence**, with due consideration to the persuasiveness of any arguments and any secondary evidence. *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). The legal standard of "a preponderance of evidence" requires the evidence to be more convincing than the evidence which is offered in opposition to it. With regard to rejections under 35 U.S.C. 103, **the examiner must provide evidence which as a whole shows that the legal determination sought to be proved (i.e., the reference teachings establish a prima facie case of obviousness) is more probable than not.**

The Examiner must weigh the Applicant's evidence presented on the record under a preponderance standard rather than an absolute standard for deciding whether there was a lack of predictability in the art at the time of filing that one of skill would not have expected to succeed in identifying viral miRNAs. Under a proper analysis, the Examiner must consider the evidence of nonobviousness that all the prior art miRNA sequences at the time of filing were evolutionary related within a few branches of the phylogenic tree[1] and the cited computational method art of Lai relies on this same sequence conservation for identifying additional miRNAs.[2] Lai's miRNA seeker program only relies on miRNA sequences conserved across bilaterian evolutionary related species and is therefore only applicable to higher multicellar organism such as worms, flies, and human. All of these computational tools for predicting miRs were based at the time of filing on a limited number of eukaryotic sequences (i.e., worm, flies, vertebrates and plants) and provide no guidance as

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[1] The Examiner has only provided prior art that demonstrates identification of miRNAs in a limited number of complex eukaryotes such as vertebrate (human, mice and rats), invertebrate animals (C. elegans, Drosophila) and plants) at the time of filing.

[2] As discussed in our response of March 16, 2009, miRseeker of Lai relies on miRNA sequences conserved across bilaterian evolutionary related species (i.e., complex eukaryotes) to identify new miRNA sequences and precursors. See page 2, first column lines 7-12; second column, lines 1 and 2 of second full paragraph; page 4, second column, first full paragraph. As concluded by Lai, "the approach used in this study should be applicable to the analysis of other sets of sequenced genomes of related higher eukaryotic model organisms." See page 17, first column, second full paragraph 11-13. Clearly, Lai is limited to the identification of miRNAs within a few small branches of the phylogenic tree-a limited number of complex eukaryotes such as vertebrate animals (humans, mice, and rats), invertebrate animals (C. elegans, Drosophila), and plants. While Lai disclose that computational method may be useful to identify new miRNAs in the genomes of highly related eukaryotes such as worms, flies, humans, and perhaps all animals, the cited references fail to state or demonstrate in any way miRNAs were expected to be present in divergent single cell organisms (such as bacteria or yeast) or acellular organisms such as fungi, let alone viruses.

to generating predictive algorithms for the divergent single cell organism (bacteria, yeast) or viral genomic sequences.

The Examiner only tangible assertion is to simply argue that there is plenty of intergenic space in HSV-1 genomic sequence for predicting the hairpin precursor and therefore overcomes the Applicant's requirement to show with absolute certainty that at the time of filing it was believe that viral miRNAs could not exist. The Examiner uses the prior art reference Perry to support the assertion that a virus such as HSV-1 contains sufficient length and space of nucleotide sequences to harbor hairpin precursors. Applicant respectfully submits that with regard to the Examiner's assertion, the frequency of predictable hairpins based on the models available at the time of filing would have predicted a frequency of less than 1 for HSV-1 as well.

HSV-1 is a double stranded DNA genome of 152,000 bps.[3] HSV-1 is nearly the same size as Epstein Barr Virus, which we stated has hairpin precursor frequency of less than one in Applicant's response of February 26, 2008. Table 1 below is presented with the addition of HSV-1 to the previously discussed Epstein Barr Viru, HCMV, and HPV using the same average hairpin frequency and highest frequency of know hairpin precursor that were known at the time of filing.[4]

Organism	Genome Size (bp)	Expected Hairpins-1 (average frequency)	Expected Hairpins-2 (highest frequency)
Virus			
Epstein Barr Virus	1.75×10^5	0.0972	0.186
HCMV	2.30×10^5	0.0128	0.243
HPV	7.91×10^3	0.000439	0.00839
HSV-1	1.52×10^5	0.00844	0.161

Even with the addition of HSV-1, Table 1 shows that less than one (1) hairpin precursor would have been expected to be present based on the average hairpin frequency in known organisms at the time of time of filing. Similarly, Column 4 lists the number of hairpin precursors that would be expected over the genomes of each virus using Applicants presented highest hairpin frequency known at the time of filing of *C. elegans* (9.43×10^5). Thus, the frequency of miRNAs/hairpins in HSV-1 is in fact worse than the frequency of Epstein Barr Virus. Applicant further submits that the viruses of Zhu,

[3] See Perry at page 1.

[4] The average frequency of known hairpins at the time of filing was 1 hairpin for every 1.80×10^7 bps as discussed in greater detail in Applicant's reply of February 26, 2008. The highest hairpin frequency Applicant presented in our reply of February 26, 2008 was 1 hairpin for every 9.43×10^5 bps in *C. elegans*.

Ghiringhelli, Baumstark, Ozdarendeli, and Davison are similarly sized as those viruses in Table 1 above and would have the same low frequency of less than one miRNA/hairpin per genome. Accordingly, Applicant respectfully submits that one of ordinary skill in the art would have not expected to be able to identify miRNAs and hairpin precursors in viruses regardless of the method of identification and HSV-1 does not dispel this notion.

Thus, the Examiner has failed on both arguments. One, the Examiner has failed to provide any concrete evidence that bridges the phylogenic gap between the cited prior art's identification of miRNAs within a few small branches of the phylogenic tree and the more divergent branches of the phylogenic tree representing single cell organisms (such as bacteria or yeast), acellular organisms (such as fungi) and viruses. Second, just because viruses may have intergenic spaces as argued by the Examiner, it does not overcome the issue of a less than 1 miRNA/hairpin frequency for viruses discussed above and in the record.

In summary, in view of the fact that miRNAs had only been isolated from species who are clustered within one region of the phylogenic tree completely divergent from viruses, the lack of predictive miRNA algorithm tools to account for viral genomic sequences, and doubts regarding the genome size vs. hairpin frequency necessary to harbor hairpin precursors in a viral genome, one of skill would not reasonably be able to predict the claimed invention and expect to succeed in identifying viral miRNAs at the timing of filing. Based on the evidence above and the inability of the Examiner to counter this evidence, Applicant has shown by a preponderance of the evidence that there was no reasonable expectation by one of ordinary skill in the art at the time of filing that miRNAs would be present in the viral genome. Applicant's extensive record as discussed above demonstrates this unpredictability, and the Examiner has failed to bridge the gap between the fatal divergence of sequence conservation between viruses and complex eukaryotes, and lack of space to harbor hairpin precursors in viral genomes. In view of the foregoing, the Applicant respectfully asserts that one of skill would not have expected to be able to identify the claimed viral miRNAs and hairpins. Accordingly, Applicant submits that the rejection of claims 21-34 and 50 under 35 U.S.C. §103(a) as being obvious over Lai in view of Zhu, Ghiringhelli, Baumstark, Ozdarendeli, Davison, and Perry has been overcome and should be withdrawn.

d. Nonstatutory Obviousness-type Double Patenting

U.S. Patent No. 7,696,334

On page 23 of the Office Action, the Examiner rejects claims 21, 33, 34, 52 and 53 on the grounds of nonstatutory obviousness-type double patenting over claims 1-6 of U.S. Patent No. 7,696,334 (U.S. Patent Appl. No. 10/604,942). The Examiner asserts the claimed broad genus claims are anticipated by the viral miRNA species claims drawn to a 24-mer of SEQ ID NO: 37405 and 116-mer of SEQ ID NO: 37404.

U.S. Patent No. 7,696,334 and the instant application are commonly owned by Rosetta Genomics Inc. Applicant submits a terminal disclaimer of the instant application signed by an authorized agent of the assignee to the '334 patent in compliance with 37 C.F.R. §1.321(c) and 37 C.F.R. §3.73(b) thereby overcoming the alleged nonstatutory double patenting rejection. In view of the foregoing terminal disclaimer, Applicant respectfully requests that the Examiner reconsider and withdraw the nonstatutory obviousness-type double patenting rejection of claims 21, 33, 34, 52 and 53 over claims 1-6 of U.S. Patent No. 7,696,334.

U.S. Patent Appl. No. 10/604,943 (In preparation for Issuance)

On page 24 of the Office Action, the Examiner rejects claims 21, 33, 34, 52 and 53 on the grounds of nonstatutory obviousness-type double patenting over claims 1-6 of U.S. Patent App. No. 10/604,943. The Examiner asserts the claimed broad genus claims are anticipated by the viral miRNA species claims drawn to a the mir/hairpin species as set forth in SEQ ID NOS: 128, 131, 133, 477, 480 and 482 respectively.

U.S. Patent Appl. No. 10/604,943 and the instant application are commonly owned by Rosetta Genomics Inc. Applicant submits a terminal disclaimer of the instant application signed by an authorized agent of the assignee to the '943 patent application in compliance with 37 C.F.R. §1.321(c) and 37 C.F.R. §3.73(b) thereby overcoming the alleged nonstatutory double patenting rejection. In view of the foregoing terminal disclaimer, Applicant respectfully requests that the Examiner reconsider and withdraw the nonstatutory obviousness-type double patenting rejection of claims 21, 33, 34, 52 and 53 over claims 1-6 of U.S. Patent Appl. No. 10/604,943.

U.S. Patent No. 7,696,342

On page 24 of the Office Action, the Examiner rejects claims 21, 33, 34, 52 and 53 on the grounds of nonstatutory obviousness-type double patenting over claims 1-6 of U.S. Patent No. 7,696,342 (U.S. Patent Appl. No. 10/604,945). The Examiner asserts the claimed broad genus

claims are anticipated by the viral miRNA species claims drawn to a 24-mer of SEQ ID NO: 5264 and 69-mer of SEQ ID NO: 2194.

U.S. Patent No. 7,396,342 and the instant application are commonly owned by Rosetta Genomics Inc. Applicant submits a terminal disclaimer of the instant application signed by an authorized agent of the assignee to the '342 patent in compliance with 37 C.F.R. §1.321(c) and 37 C.F.R. §3.73(b) thereby overcoming the alleged nonstatutory double patenting rejection. In view of the foregoing terminal disclaimer, Applicant respectfully requests that the Examiner reconsider and withdraw the nonstatutory obviousness-type double patenting rejection of claims 21, 33, 34, 52 and 53 over claims 1-6 of U.S. Patent No. 7,696,342.

U.S. Patent Appl. No. 10/604,984 (In preparation for Issuance)

On page 24 of the Office Action, the Examiner rejects claims 21, 33, 34, 52 and 53 on the grounds of nonstatutory obviousness-type double patenting over claims 1-6 of U.S. Patent App. No. 10/604,984. The Examiner asserts the claimed broad genus claims are anticipated by the viral miRNA species claims drawn to a the mir/hairpin species as set forth in SEQ ID NO: 4642 and SEQ ID NO: 1917 respectively.

U.S. Patent Appl. No. 10/604,984 and the instant application are commonly owned by Rosetta Genomics Inc. Applicant submits a terminal disclaimer of the instant application signed by an authorized agent of the assignee to the '984 patent application in compliance with 37 C.F.R. §1.321(c) and 37 C.F.R. §3.73(b) thereby overcoming the alleged nonstatutory double patenting rejection. In view of the foregoing terminal disclaimer, Applicant respectfully requests that the Examiner reconsider and withdraw the nonstatutory obviousness-type double patenting rejection of claims 21, 33, 34, 52 and 53 over claims 1-6 of U.S. Patent Appl. No. 10/604,984.

U.S. Patent No. 7,217,807

On page 24 of the Office Action, the Examiner rejects claim 53 on the grounds of nonstatutory obviousness-type double patenting over claims 2 of U.S. Patent No. 7,217,807. The Examiner asserts the claimed broad genus claims are anticipated by the viral miRNA species claims drawn to a 77-mer of SEQ ID NO: 14.

U.S. Patent No. 7,217,807 and the instant application are commonly owned by Rosetta Genomics Inc. Applicant submits a terminal disclaimer of the instant application signed by an authorized agent of the assignee to the '807 patent in compliance with 37 C.F.R. §1.321(c) and 37

C.F.R. §3.73(b) thereby overcoming the alleged nonstatutory double patenting rejection. In view of the foregoing terminal disclaimer, Applicant respectfully requests that the Examiner reconsider and withdraw the nonstatutory obviousness-type double patenting rejection of claim 53 over claim 2 of U.S. Patent No. 7,217,807.

U.S. Patent Appl. No. 10/709,739; 11/511,035; and 12/517,760

On pages 24 and 25 of the Office Action ,the Examiner provisionally rejects claims 21, 33, 34, 52, and 53 on the grounds of nonstatutory obviousness-type double patenting over claims 26, 31, 33, and 35-37 of 10/709,739, claims 20, 22, 26, and 28-30 of 11/511,035, and claims 26-28 of 12/517,760.

Applicant respectfully requests that the Examiner hold the rejection in abeyance until there is allowable subject matter, at which time Applicant will consider the claims in U.S. Patent Appl. Nos. 10/709,739, 11/511,035, and 12/517,760 or file a terminal disclaimer.

3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

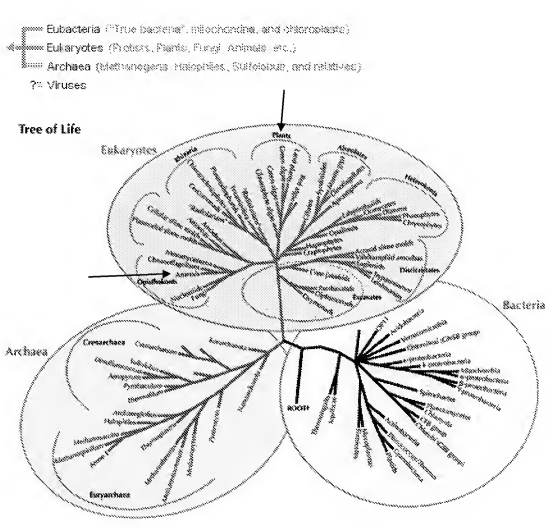
POLSINELLI SHUGHART PC

Dated: May 11, 2010

By: /Teddy C. Scott, Jr./
Teddy C. Scott, Jr., Ph.D.
Registration No. 53,573
Customer No. 37808

POLSINELLI SHUGHART PC
180 N. Stetson Ave., Suite 4525
Chicago, IL 60601
312.819.1900 (main)
312.873.3955 (E-fax)
312.873.3613 (direct)

APPENDIX A


Eubacteria ("True bacteria", mitochondria, and chloroplasts)
Eukaryotes (Protists, Plants, Fungi, Animals, etc.)
Archaea (Methanogens, Halophiles, Sulfolobus, and relatives)
?= Viruses
Tree of Life
Eukaryotes
Plants
Alveolates
Heterokonts
Opisthokonts
Dictyostelids
Bacteria
Archaea
Crenarchaea
ROOT
Euryarchaea